REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim Amendments

Claims 4, 6, 7, 15-17, 23-27, and 30-33 currently are pending.

Claims 1-3, 8-14, 18-22, and 28-29 stand canceled. Claim 5 has now been canceled. Claim 5 has been incorporated into claim 4.

Claims 4 and 6 have been amended to remove a typographical error. Claim 4 has further been amended to incorporate the phrase "wherein at least one of R and R^1 is other than hydrogen," from claim 5. Claims 15, 17, 31, and 32 are currently amended to remove their claim dependencies from now canceled claim 5. Claim 23 is being amended to correct its claim dependency. Claims 32 and 33 have been amended to remove the phrase "or at risk of developing HCV." No new matter has been added by these amendments. Cancellation of the subject matter is not intended to be a dedication of the canceled subject matter to the public. Applicants reserve the right to file a continuation application directed to the canceled subject matter.

Claims 4, 6-7, 15-17, 23-27, and 30-33 currently are under consideration.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claim objection under 35 C.F.R. §1.75(c)

The Office has objected to claim 23 under 37 C.F.R. § 1.75(c) as being in improper dependent form because a claim cannot depend from a canceled claim. *See* page 2 of the Office Action.

Applicants have amended claim 23 to correct the claim dependency. Withdrawal of this objection is respectfully requested.

Claim rejection under 35 U.S.C. §112, first paragraph

The Office has rejected claims 4-7, 15-17, 24-27 and 30-33 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office specifically states that, "[a]pplicant has provided at pages 56-69 and 76-79 a total of 9 examples and has provided only exemplary proposed testing of the compounds claimed, but to date has provided no test data in support of the theory that many of the instant claimed compounds has pharmaceutical activity.... As a consequence of these amendments applicant has provided a panoramic view of a vast generic class of compounds wherein there is a very little synthetic guidance (9 examples) and only prospective guidance in the area of medicinal testing." The Office further states that the Applicant's terminology in claims 32 and 33 suggesting –prevention-(the treatment of "hosts at risk of developing HCV") is completely unsupported by even a prospective testing protocol. *See* pages 2-3 of the Office Action.

As summarized in the MPEP § 2163, "[t]he first paragraph of 35 U.S.C. § 112 requires that the 'specification shall contain a written description of the invention * * *.' This requirement is separate and distinct from the enablement requirement." The test for written description requirement is whether an applicant conveys with reasonable clarity to those skilled in the art

that, as of the filing date sought, he or she was in possession of the invention claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by the disclosure of drawings or structural chemical formulas that show that the applicant was in possession of the claimed invention. MPEP § 2163(II)(A)(3). The written description requirement for a chemical genus "requires a precise definition, such as by structure, formula, or chemical name," of the claimed subject matter sufficient to distinguish it from other material. *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). MPEP § 2163(II)(A)(3) states that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

In order to make a rejection based on this requirement, the Office has the initial burden, after a thorough reading and evaluation of the content of the application, of presenting evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. See MPEP 2163.01(III)(A) (citing *In re Wertheim*, 541 F.2d 257, 262; 191 USPQ 90, 96 (CCPA 1976)). There is a presumption that an adequate written description of the claimed invention is present in the specification as filed. *Id.* (citing *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971)).

Applicants submit that the Office has not met its burden to show that there is inadequate written description and further submit that the instant application describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Claims 4, 6, 7 are directed to a genus of chemical compounds. As required by *Eli Lilly* and the MPEP, the claims clearly set forth the chemical structures of compounds fall in the

scope of the claims by reduction to drawings of chemical structures coupled with detailed descriptions of all elements recited in the structures. The Office has not provided any reason or evidence that a person of ordinary skill in the chemical art looking at these structures and definitions would not recognize that Applicants were in possession of the claimed invention—compounds represented by the generic structures. The Office, however, alleges that the application only provided nine examples and provided no test data in support of the compounds' pharmaceutical activity. Applicants submit that such assertions do not support a finding of inadequate written description.

The instant application provides Examples 1-32 on pages 65-86 showing procedures for preparing more than just nine specific exemplified compounds. The instant application further describes in Biological Example 1 on pages 86-87 various assays that are available in literature that can be used to assess the activities of the compounds. Biological Example 2 on pages 87-88 further describes a Replicon whole cell assay. Biological Example 3 on page 88 describes cloning and expression of recombinant HCV-NS5b for use in the HCV-NS5b enzyme assay of Biological Example 4 on pages 88-89.

By requiring more examples and testing results, the Office Action apparently equates "written description" to "reduction to practice." Reduction to practice is only one of the methods to satisfy the written description requirement. *See* MPEP § 2163(II)(3). Applicants submit that the written description requirement is satisfied because there is sufficient structural description of the claimed genus as a whole. Based on the knowledge and skill known in the art and the disclosure provided in the instant application, it is clear to one skilled in the art that the inventors were in the possession of the claimed subject matter.

In order to expedite prosecution, Applicants have canceled the phrase, "hosts at risk of developing HCV" in claim 32 and 33 in response to the Office's objection to the phrase.

Withdrawal of this rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

Claim rejection under 35 U.S.C. §112, first paragraph

The Office has rejected claims 4-7, 15-17, 24-27 and 30-33 under 35 U.S.C. §112, first paragraph, alleging that the specification does not reasonably provide enablement for the vast array of compounds now claimed with Markush group listings where some terms are entirely generic (e.g. "lipids," "carbohydrates," "peptides," "amino acids," etc.). *See* page 3 of the Office Action. The Office Action alleges that undue experimentation is required to practice the full scope of the claimed invention.

With respect to the specific Wands factors raised by the Office Action, Applicants provide the following response and observations:

(A) The breadth of the claims

The Office objects to generic terms such as "lipids," "carbohydrates," "peptides," and "amino acids" as used in the claims, Applicants submit that instant application defines these terms on pages 42-43 of the application as filed. For example, the term "amino acid" has been defined as α-amino acids of the formula $NH_2CH(R^7)COOH$ where R^7 is hydrogen, alkyl, substituted alkyl or aryl (page 42, lines 16-18 of the application as filed). Therefore, "amino acid" as used in the instant claims is bound by the limits of the definition as defined in the specification.

A person skilled in the art would understand that a carboxylic acid group, e.g. the COOH group in $NH_2CH(R^7)COOH$, can form an ester bond with a hydroxy group of the ribonucleosides (as in Formulas IB, IC and IC-A) under conventional esterification conditions. Similarly, terms "lipids," "carbohydrates," and "peptides," have also been defined in the application on pages 42-43 and can be coupled to a hydroxy group (as in Formulas IB, IC and IC-A) via an ester or an ether bond, the formation of which is generally known the art. The instant application therefore provides sufficient disclosure commensurate with the scope of the protection sought by the

claims and one skilled in the art can make and use the scope of the claimed invention without undue experimentation.

(B, C, and D) The nature of the invention, state of the prior art and level of skill in the art

Applicants agree that one of skill in the art would be knowledgeable in the art of organic synthesis and in the art of determination of medicinally appropriate dosages in the treatment of HCV (*see* page 4, point D of the Office Action). As such one skill would be able to recognize, for example with respect to the synthesis of the compounds, that the claimed nucleosides provide free 2', 3', and 5' hydroxyl groups that can be manipulated with well known synthetic procedures to arrive at the claimed compounds with substitutions at those groups.

(E) The predictability or unpredictability of the art

Applicants note that many assays that test for activity against flaviviridae viruses known, and some of those assays are provided in the Biological examples on pages 86-89. Further various clinical methodologies are also known, as evidenced by the large number of clinical trials currently in progress relating to the treatment of hepatitis C. Therefore, while analysis of just a chemical structure may not be easily predictive of efficacy, results developed from the *in vitro*, *in vivo* and clinical tools available to one of ordinary skill in the art would be reasonably predictive of success in treating an HCV infection. Also, given the level of skill for the skilled artisan as noted above, the use and interpretation of such *in vitro* and *in vivo* assays would be relatively routine resulting in a high level of predictability.

(F) the amount of direction or guidance presented

The application provides synthetic Examples 1-32 on pages 65-86 and not just the 9 examples that the Office has pointed out. In addition, although its product is not covered by the claims, Example 26 on pages 76-78 shows an illustrative procedure of preparing triphosphates of hydroxylamine substituted purines. The application also provides general synthetic schemes and cited literature references on pages 45 to 60. The application also provides directions for the use

of known assays in the Biological examples to determine the activities of the claimed compounds.

(G) the presence or absence of working examples

It is well established that "there is no magical relation between the number of representative examples and the breadth of the claims; the number and variety of examples are irrelevant if the disclosure is 'enabling.'" *In re Borkowski*, 422 F.2d 904, 909, 164 USPQ 642, 646 (CCPA 1970). Further, as the Federal Circuit stated in a fundamental case on enablement, *In re Vaeck*, "the first paragraph of § 112 requires nothing more than objective enablement ... How such teaching is set forth, either by the use of illustrative examples or broad terminology, is irrelevant." *In re Vaeck*, 947 F.2d 488, 496, n.23, 20 USPQ2d 1438, 1445, n.23 (Fed. Cir. 1991). As previously noted, the preparation of specific compounds are exemplified in Examples 1-32. While no actual data is presented for the claimed compounds, the specification clearly provides detailed direction to one of ordinary skill in the art to generate such data (see Biological Examples on pages 86-89).

(H) the quantity of experimentation necessary

As discussed above, the specification provides several methods of assaying anti-viral activity, including the replicon assay and HCV-NS5b enzyme assay. Performing any or all of the assays described would not require any undue experimentation. Thus, it would require nothing more than routine experimentation of an ordinarily skilled artisan to use a compound, in any one of these assays.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987). The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI*

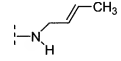
Int'l v. Matsushita Elec. Corp. of America, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed.Cir. 1985). Given the explicit disclosure the of the synthesis of the compounds and of the known methods for assessing the anti-viral activity, Applicants submit that the claims are fully enabled.

Claim rejection under 35 U.S.C. §112, second paragraph

The Office has rejected claims 4-7, 15-17, 24-27 and 30-33 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention.

A. The Office specifically points to claim 4 at line 20, the group NR^3R^4 wherein R^3 and R^4 may be "alkenyl" or "alkynyl," as unlikely to be stable or easily isolable. The Office further points to many of the Markush groups to be boilerplate and not as examples of any utility. *See* page 5 of the Office Action.

Applicants note that the group NR^3R^4 wherein R^3 and R^4 may be "alkenyl" or "alkynyl" include the substituent exemplified below:[1]



The terms "alkenyl" and "alkynyl" have been defined in the specification on page 37, lines 20-23, and page 38, lines 3-5. For example, "alkenyl" has been defined as preferably having 2 to 6 carbon atoms and more preferably 2 to 4 carbon atoms and having at least 1 and preferably from 1-2 sites of alkenyl unsaturation. Such an alkenyl substitution on the N of the NR^3R^4 would not necessarily lead to an unstable compound. The Office's assertion that such compounds are unlikely to be stable or easily isolable is merely speculation. Applicants request the Office to provide a reference to support the argument.

[1] The structure is for explanation purposes only and is not intended to limit the scope of the claim.

The Office further alleges that many of the Markush groups in the claims to be boilerplate and not as examples of any utility. Applicants respectfully submit that the substituents listed in the Markush groups are necessary in order to fully define Applicants' invention and there is no statutory basis to reject a claim based on an alleged use of a boilerplate language. Further, Applicants respectfully request the Office specifically point out the substituents that the Office construes as boilerplate or "deadwood" or not of any utility and provide support for any such assertions.

Withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

B. The Office specifically points to claim 4 at lines 54-64, where a Markush group has been defined with the generic names of the classes of compounds. *See* page 5 of the Office Action.

The Office points to generic terms like "lipids," "carbohydrates," "peptides," "amino acids," being used as a substituent W, W^2, and W^3 in the claims. The instant application defines these terms on pages 42-43 of the application as filed. For example, the term "amino acid" has been defined as α-amino acids of the formula $NH_2CH(R^7)COOH$ where R^7 is hydrogen, alkyl, substituted alkyl or aryl (page 42, lines 16-18 of the application as filed). Therefore, "amino acid" as used in the instant claims is bound by the limits of the definition as defined in the specification. Similarly, terms "lipids," "carbohydrates," and "peptides," have also been defined in the application on pages 42-43. Therefore, these substituents are attached as a W via their hydroxyl end or a carboxylic end, as is appropriate, to the –OW in claim 4. The use of these terms in the claims does not render the claims indefinite.

Withdrawal of this rejection as claim being indefinite is respectfully requested.

C. The Office objects to the term "and or" at the end of the line in claim 4 at line 68. The office suggests cancellation of the term "and." *See* page 5 of the Office Action.

Applicants have canceled the term "and" as suggested. Withdrawal of this rejection is respectfully requested.

D. The Office has rejected claim 6 stating that in claim 6 at line 53, the term "(-S or R Inactive)" is unclear concerning what applicant has intended to claim. *See* page 5 of the Office Action.

Applicants have canceled the term "(-S or R Inactive)" as suggested. Withdrawal of this rejection is respectfully requested.

E. The Office has rejected claims 32 and 33 stating that the term "host" is incomplete and should be amended to read "host in need thereof." *See* page 6 of the Office Action.

Applicants have amended claims 32 and 33 to incorporate the phrase as suggested by the Office. Withdrawal of this rejection is respectfully requested.

Claim rejection under 35 U.S.C. §102(b)

The Office has rejected claims 4, 24-26 and 31 under 35 U.S.C. §102(b) as being anticipated by Knutsen et al. (US Patent 5,430,027). The Office specifically refers to columns 12-16, titled Example compounds 4-9 and 12 and at column 17-18, claims 1-2, 4-7, 9, and 12-15 wherein allegedly the instant claimed subject matter has been anticipated. *See* page 6 of the Office Action.

To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1379 (Fed. Cir. 1986). In order to expedite prosecution, Applicants have amended claim 4 to incorporate the phrase "wherein at least one of R and R^1 is other than hydrogen," from claim 5. None of the titled Example compounds 4-9 and 12 or column 17-18, claims 1-2, 4-7, 9, and 12-15 of Knutsen *et al.* correspond to a 2' or 3'-C-substituted-ribofuranosyl ring as in instant claims. Applicants believe

that this rejection under 35 U.S.C. §102(b) as being anticipated by Knutsen *et al.* is now moot and is requested to be withdrawn.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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